

AMENDMENTS TO SPECIFICATION

Insert the following paragraph after the title and before the first paragraph at page 1 of the specification:

This application is a 35 USC 371 national stage application of International application PCT/JP03/04437, filed April 8, 2003, for which priority is claimed pursuant to 35 USC 119 based on Japanese application 2002-105021, filed April 8, 2002, and Japanese application 2002-172678, filed June 13, 2002.

Amend the paragraph beginning at line 14 of page 26 as follows:

As the hydrolase to be used in the hydrolysis of the present invention, there may be mentioned, for example, protease, esterase, lipase and the like, preferably a lipase of microorganisms which are capable of isolating from yeast or bacteria, more preferably a lipase originated from *Pseudomonas* (for example, ~~Amano~~ AMANO PS (available from Amanoenzyme Co.), etc.), a lipase originated from *Candida antarctica* (for example, ~~Chirazyme~~ CHIRAZYME L-2 (available from Roche AG), etc.), particularly preferably a lipase originated from *Candida antarctica* is used. Incidentally, these hydrolases may be used in a natural form or a commercially available product as such as a fixed enzyme, and may be used alone or in combination of two or more kinds.

Amend the paragraph beginning at line 20 of page 57 and ending at line 9 of page 58 as follows:

To 2 mL of a 0.1 mol/L aqueous sodium phosphate solution with a pH of 8.0 was added 100 mg of methyl (±)-3-benzylamino-4-methylpentanoate, and the mixture was maintained at 30°C. To the resulting mixture was added 1 mg of lipase (CAL; available from Roche, ~~Chirazyme~~ CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 45 minutes, at the time when the conversion rate of the starting materials reached 49.9%, 2 mol/L of hydrochloric acid was added to the reaction mixture to adjust a pH to 1, then, the mixture was filtered through Celite (No. 545), and washed with 5 ml of chloroform. To the resulting filtrate was added 20 ml of chloroform whereby the product and the starting material were extracted. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and after filtration, the organic layer was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica gel column chromatography (~~Wakogel~~ WAKOGEL C-200 (trade name), chloroform/ methanol=98/2 to 80/20 (volume ratio)) to obtain 42.0 mg (Isolated yield based on methyl (±)-3-benzylamino-4-methylpentanoate=42.0%) of methyl (R)-3-benzylamino-4-methylpentanoate and 37.7 mg (Isolated yield based on methyl (±)-3-benzylamino-4-methylpentanoate=39.8%) of (S)-3-benzylamino-4-methylpentanoic acid.

Amend the paragraph beginning at line 18 and ending at line 33 of page 58 as follows:

Analytical conditions of high performance liquid chromatography;

Methyl 3-benzylamino-4-methylpentanoate

Column: ~~chiral pack~~ CHIRAL PACK AS (0.46 cm Φ x 25 cm, available from DAICEL
CHEMICAL INDUSTRIES, LTD.)

Solvent: hexane/isopropyl alcohol (=9/1 (volume ratio))

Flow rate: 0.5 ml/min

Temperature: 30°C

3-Benzylamino-4-methylpentanoic acid

Column: ~~chiral~~ CHIRAL CD-Ph (0.46 cm Φ x 25 cm, available from SHISEIDO CO., LTD.)

Solvent: acetonitrile/water (=1/9 (volume ratio))

Potassium dihydrogen phosphate 40 mM

pH 3.5

Flow rate: 0.5 ml/min

Temperature: 25°C

Amend the paragraph beginning at line 22 of page 59 and ending at line 11 of page 60 as follows:

Incidentally, absolute configuration of an optically active methyl 3-benzylamino-4-methylpentanoate was determined as follows. That is, 202 mg of optically active methyl 3-

benzylamino-4-methylpentanoate having an optical purity of 99.9%ee or more obtained by the same procedures as in Example 1 was dissolved in 2 mL of methanol, 22.8 mg of 20% palladium/carbon powder was added to the solution, and the mixture was reacted at room temperature while stirring. After 1 hour, the reaction mixture was filtered through Celite (No. 545), and washed with 5 ml of methanol. The resulting filtrate was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica gel column chromatography (~~Wakogel~~ WAKOGEL C-200 (trade name), chloroform/methanol=98/2 to 0/100 (volume ratio)) to obtain 100 mg (Isolated yield based on optically active methyl 3-benzylamino-4-methylpentanoate=90.0%) of optically active 3-amino-4-methylpentanoic acid. Absolute configuration was determined by comparing a specific rotatory power ($[\alpha]_D^{23} +27.8^\circ$ (C 0.20, MeOH)) of the resulting optically active 3-amino-4-methylpentanoic acid and a sign (literal value $[\alpha]_D^{25} -28.2^\circ$ (C 0.48, MeOH)) of a specific rotatory power of (R)-3-amino-4-methylpentanoic acid described in Tetrahedron (Tetrahedron., 51 (45), 12237 (1995)).

Example 2 (Syntheses of methyl (R)-3-benzylamino-4-methylpentanoate and (S)-3-benzylamino-4-methylpentanoic acid)

Amend the paragraph beginning at line 12 and ending at line 36 of page 60 as follows:

To a mixed solvent of 1 mL of cyclohexane and 1 mL of water was added 100 mg of methyl (\pm)-3-benzylamino-4-methylpentanoate, and the mixture was maintained at 30°C. To the resulting mixture was added 1 mg of lipase (CAL; available from Roche, ~~Chirazyme~~ CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature,

and the mixture was reacted at 30°C while stirring. After 100 minutes, at the time when the conversion rate of the starting materials reached 50.0%, 2 mol/L of hydrochloric acid was added to the reaction mixture to adjust a pH to 1, filtered through Celite (No. 545), and washed with 5 ml of chloroform. To the resulting filtrate was added 20 mol of chloroform, and the product and the starting materials were extracted. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and after filtration, the organic layer was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica gel column chromatography (~~Wakogel~~ WAKOGEL C-200 (trade name), chloroform/methanol=98/2 to 80/20 (volume ratio)) to obtain 45.0 mg (Isolated yield based on methyl (±)-3-benzylamino-4-methylpentanoate=45.0%) of methyl (R)-3-benzylamino-4-methylpentanoate and 41.9 mg (Isolated yield based on methyl (±)-3-benzylamino-4-methylpentanoate=44.6%) of (S)-3-benzylamino-4-methylpentanoic acid.

Amend the paragraph beginning at line 9 and ending at line 24 of page 61 as follows:

Analytical conditions of high performance liquid chromatography;

Methyl 3-benzylamino-4-methylpentanoate

Column: ~~chiral-pack~~ CHIRAL PACK AS (0.46 cmΦ x 25 cm, available from DAICEL
CHEMICAL INDUSTRIES, LTD.)

Solvent: hexane/isopropyl alcohol (=9/1 (volume ratio))

Flow rate: 0.5 ml/min

Temperature: 30°C

3-Benzylamino-4-methylpentanoic acid

Column: ~~ehiral~~ CHIRAL CD-Ph (0.46 cm Φ x 25 cm, available from SHISEIDO CO., LTD.)

Solvent: acetonitrile/water (=1/9 (volume ratio))

Potassium dihydrogen phosphate 40 mM

pH 3.5

Flow rate: 0.5 ml/min

Temperature: 25°C

Amend the paragraph beginning at line 29 of page 61 and ending at line 16 of page 62 as follows:

To a mixed solvent of 5 mL of cyclohexane and 5 mL of water was added 1 g of methyl (\pm)-3-benzylamino-4-methylpentanoate, and the mixture was maintained at 30°C. To the resulting mixture was added 1 mg of lipase (CAL; available from Roche, Chirazyme CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 10 hours, at the time when the conversion rate of the starting materials reached 50.2%, 2 mol/L of hydrochloric acid was added to the reaction mixture to adjust a pH to 1, filtered through Celite (No. 545), and washed with 10 ml of chloroform. To the resulting filtrate was added 20 ml of chloroform, and the product and the starting materials were extracted. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and after filtration, the organic layer was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica

gel column chromatography (~~Wakogel~~ WAKOGEL C-200 (trade name), chloroform/methanol=98/2 to 80/20 (volume ratio)) to obtain 492 mg (Isolated yield based on methyl (±)-3-benzylamino-4-methylpentanoate=49.2%) of methyl (R)-3-benzylamino-4-methylpentanoate and 443 mg (Isolated yield based on methyl (±)-3-benzylamino-4-methylpentanoate=47.1%) of (S)-3-benzylamino-4-methylpentanoic acid.

Amend the paragraph beginning at line 25 of page 62 and ending at line 4 of page 63 as follows:

Analytical conditions of high performance liquid chromatography;
Methyl 3-benzylamino-4-methylpentanoate
Column: ~~ehiral-pack~~ CHIRAL PACK AS (0.46 cmΦ x 25 cm, available from DAICEL CHEMICAL INDUSTRIES, LTD.)
Solvent: hexane/isopropyl alcohol (=9/1 (volume ratio))
Flow rate: 0.5 ml/min
Temperature: 30°C
3-Benzylamino-4-methylpentanoic acid
Column: ~~ehiral~~ CHIRAL CD-Ph (0.46 cmΦ x 25 cm, available from SHISEIDO CO., LTD.)
Solvent: acetonitrile/water (=1/9 (volume ratio))
Potassium dihydrogen phosphate 40 mM
pH 3.5
Flow rate: 0.5 ml/min

Temperature: 25°C

Amend the paragraph beginning at line 9 and ending at line 32 of page 63 as follows:

To 2 mL of a 0.1 mol/L aqueous sodium phosphate solution with a pH of 8.0 was added 100 mg of methyl (±)-3-benzylaminopentanoate, and the mixture was maintained at 30°C. To the resulting mixture was added 1 mg of lipase (CAL; available from Roche, Chirazyme CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 10 minutes, at the time when the conversion rate of the starting materials reached 47.5%, 2 mol/L of hydrochloric acid was added to the reaction mixture to adjust a pH to 1, filtered through Celite (No. 545), and washed with 5 ml of chloroform. To the resulting filtrate was added 20 ml of chloroform, and the product and the starting materials were extracted. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and after filtration, the organic layer was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica gel column chromatography (~~Wakogel~~ WAKOGEL C-200 (trade name), chloroform/methanol=98/2 to 80/20 (volume ratio)) to obtain 45.4 mg (Isolated yield based on methyl (±)-3-benzylaminopentanoate=45.4%) of methyl (S)-3-benzylaminopentanoate and 39.8 mg (Isolated yield based on methyl (±)-3-benzylaminopentanoate=42.5%) of (R)-3-benzylaminopentanoic acid.

Amend the paragraph beginning at line 5 and ending at line 20 of page 64 as follows:

Analytical conditions of high performance liquid chromatography;

Methyl 3-benzylaminopentanoate

Column: ~~chiral pack~~ CHIRAL PACK AS (0.46 cm Φ x 25 cm, available from DAICEL
CHEMICAL INDUSTRIES, LTD.)

Solvent: hexane/isopropyl alcohol (=9/1 (volume ratio))

Flow rate: 0.5 ml/min

Temperature: 30°C

3-Benzylaminopentanoic acid

Column: ~~chiral~~ CHIRAL CD-Ph (0.46 cm Φ x 25 cm, available from SHISEIDO CO., LTD.)

Solvent: acetonitrile/water (=1/9 (volume ratio))

Potassium dihydrogen phosphate 40 mM

pH 3.5

Flow rate: 0.5 ml/min

Temperature: 25°C

Amend the paragraph beginning at line 8 and ending at line 31 of page 65 as follows:

To a mixed solvent of 1 mL of cyclohexane and 1 mL of water was added 100 mg of methyl (\pm)-3-benzylaminopentanoate, and the mixture was maintained at 30°C. To the resulting mixture was added 1 mg of lipase (CAL; available from Roche, ~~Chirazyme~~ CHIRAZYME L-2

(trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 30 minutes, at the time when the conversion rate of the starting materials reached 50.6%, 2 mol/L of hydrochloric acid was added to the reaction mixture to adjust a pH to 1, filtered through Celite (No. 545), and washed with 5 ml of chloroform. To the resulting filtrate was added 20 mol of chloroform, and the product and the starting materials were extracted. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and after filtration, the organic layer was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica gel column chromatography (~~Wakogel~~ WAKOGEL C-200 (trade name), chloroform/methanol=98/2 to 80/20 (volume ratio)) to obtain 46.2 mg (Isolated yield based on methyl (±)-3-benzylaminopentanoate=46.2%) of methyl (S)-3-benzylaminopentanoate and 40.3 mg (Isolated yield based on methyl (±)-3-benzylaminopentanoate=43.0%) of (R)-3-benzylaminopentanoic acid.

Amend the paragraph beginning at line 4 and ending at line 19 of page 66 as follows:

Analytical conditions of high performance liquid chromatography;

Methyl 3-benzylaminopentanoate

Column: ~~chiral pack~~ CHIRAL PACK AS (0.46 cmΦ x 25 cm, available from DAICEL CHEMICAL INDUSTRIES, LTD.)

Solvent: hexane/isopropyl alcohol (=9/1 (volume ratio))

Flow rate: 0.5 ml/min

Temperature: 30°C

3-Benzylaminopentanoic acid

Column: ~~chiral~~ CHIRAL CD-Ph (0.46 cmΦ x 25 cm, available from SHISEIDO CO., LTD.)

Solvent: acetonitrile/water (=1/9 (volume ratio))

Potassium dihydrogen phosphate 40 mM

pH 3.5

Flow rate: 0.5 ml/min

Temperature: 25°C

Amend the paragraph beginning at line 24 of page 66 and ending at line 14 of page 67 as follows:

To a mixed solvent of 1 mL of cyclohexane and 1 mL of water was added 100 mg of methyl (±)-3-benzylaminobutyrate, and the mixture was maintained at 30°C. To the resulting mixture was added 0.1 mg of lipase (CAL; available from Roche, ~~Chirazyme~~ CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 4.5 hours, at the time when the conversion rate of the starting materials reached 52.6%, 2 mol/L of hydrochloric acid was added to the reaction mixture to adjust a pH to 1, and 20 ml of chloroform was added to the mixture to extract the starting materials. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and after filtration, the organic layer was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica gel column

chromatography (Wakogel WAKOGEL C-200 (trade name), chloroform/ methanol=98/2 to 80/20 (volume ratio)) to obtain 42.8 mg (Isolated yield based on methyl (\pm)-3-benzylaminobutyrate= 42.8%) of methyl (S)-3-benzylaminobutyrate. On the other hand, the aqueous layer which contains the product was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica gel column chromatography (Wakogel WAKOGEL C-200 (trade name), chloroform/methanol=80/20 (volume ratio)) to obtain 40.0 mg (Isolated yield based on methyl (\pm)-3-benzylaminobutyrate=43.0%) of (R)-3-benzylaminobutyric acid.

Amend the paragraph beginning at line 24 and ending at line 31 of page 67 as follows:

Analytical conditions of high performance liquid chromatography;

Methyl 3-benzylaminobutyrate

Column: ~~chiral pack~~ CHIRAL PACK AS (0.46 cm Φ x 25 cm, available from DAICEL CHEMICAL INDUSTRIES, LTD.)

Solvent: hexane/isopropyl alcohol (=9/1 (volume ratio))

Flow rate: 0.5 ml/min

Temperature: 30°C

Amend the paragraph beginning at line 20 of page 68 and ending at line 8 of page 69 as follows:

To 10 mL of 0.1 mol/L aqueous sodium phosphate solution with a pH of 8.0 was added 1.00 g of methyl (\pm)-3-benzylamino-3-phenylpropionate, and the mixture was maintained at 30°C. To the resulting mixture was added 10 mg of lipase (CAL; available from Roche, ~~Chirazyme~~ CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 23 hours, at the time when the conversion rate of the starting materials reached 49.6%, 2 mol/L of hydrochloric acid was added to the reaction mixture to adjust a pH to 1, filtered through Celite (No. 545), and washed with 10 ml of chloroform 10 ml. To the resulting filtrate was added 20 mol of chloroform, and the product and the starting materials were extracted. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and after filtration, the organic layer was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica gel column chromatography (~~Wakogel~~ WAKOGEL C-200 (trade name), chloroform/methanol=98/2 to 80/20 (volume ratio)) to obtain 438 mg (Isolated yield based on methyl (\pm)-3-benzylamino-3-phenylpropionate=43.8%) of methyl (R)-3-benzylamino-3-phenylpropionate and 410 mg (Isolated yield based on methyl (\pm)-3-benzylamino-3-phenylpropionate=43.2%) of (S)-3-benzylamino-3-phenylpropionic acid.

Amend the paragraph beginning at line 17 and ending at line 32 of page 69 as follows:

Analytical conditions of high performance liquid chromatography;

Methyl 3-benzylamino-3-phenylpropionate

Column: ~~chiral-pack~~ CHIRAL PACK AS (0.46 cmΦ x 25 cm, available from DAICEL
CHEMICAL INDUSTRIES, LTD.)

Solvent: hexane/isopropyl alcohol (=9/1 (volume ratio))

Flow rate: 0.5 ml/min

Temperature: 30°C

3-Benzylamino-3-phenylpropionic acid

Column: ~~chiral~~ CHIRAL CD-Ph (0.46 cmΦ x 25 cm, available from SHISEIDO CO., LTD.)

Solvent: acetonitrile/water (=1/9 (volume ratio))

Potassium dihydrogen phosphate 40 mM

pH 3.5

Flow rate: 0.5 ml/min

Temperature: 25°C

Amend the paragraph beginning at line 17 of page 70 and ending at line 5 of page 71 as follows:

To a mixed solvent of 1 mL of cyclohexane and 1 mL of water was added 100 mg of methyl (+)-3-benzylamino-3-phenylpropionate and the mixture was maintained at 30°C. To the

resulting mixture was added 5 mg of lipase (CAL; available from Roche, ~~Chirazyme~~ CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 31 hours, at the time when the conversion rate of the starting materials reached 48.9%, 2 mol/L of hydrochloric acid was added to the reaction mixture to adjust a pH to 1, filtered through Celite (No. 545), and washed with 5 ml of chloroform. To the resulting filtrate was added 20 ml of chloroform, and the product and the starting materials were extracted. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and after filtration, the organic layer was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica gel column chromatography (~~Wakogel~~ WAKOGEL C-200 (trade name), chloroform/methanol=98/2 to 80/20 (volume ratio)) to obtain 41.6 mg (Isolated yield based on methyl (±)-3-benzylamino-3-phenylpropionate=41.6%) of methyl (R)-3-benzylamino-3-phenylpropionate and 40.2 mg (Isolated yield based on methyl (±)-3-benzylamino-3-phenylpropionate=42.4%) of (S)-3-benzylamino-3-phenylpropionic acid.

Amend the paragraph beginning at line 14 and ending at line 29 of page 71 as follows:

Analytical conditions of high performance liquid chromatography;

Methyl 3-benzylamino-3-phenylpropionate

Column: ~~chiral pack~~ CHIRAL PACK AS (0.46 cmΦ x 25 cm, available from DAICEL CHEMICAL INDUSTRIES, LTD.)

Solvent: hexane/isopropyl alcohol (=9/1 (volume ratio))

Flow rate: 0.5 ml/min

Temperature: 30°C

3-Benzylamino-3-phenylpropionic acid

Column: ~~chiral~~ CHIRAL CD-Ph (0.46 cmΦ x 25 cm, available from SHISEIDO CO., LTD.)

Solvent: acetonitrile/water (=1/9 (volume ratio))

Potassium dihydrogen phosphate 40 mM

pH 3.5

Flow rate: 0.5 ml/min

Temperature: 25°C

Amend the paragraph beginning at line 35 at page 71 and ending at line 24 at page 72 as follows:

To 2 mL of a 0.1 mol/L aqueous sodium phosphate solution with a pH of 8.0 was added 100 mg of methyl (±)-3-benzylamino-3-(4-fluorophenyl)propionate and the mixture was maintained at 30°C. To the resulting mixture was added 5 mg of lipase (CAL; available from Roche, Chirazyme CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 4.5 hours, at the time when the conversion rate of the starting materials reached 50.4%, 2 mol/L of hydrochloric acid was added to the reaction mixture to adjust a pH to 1, filtered through Celite (No. 545), and washed with 5 ml of chloroform. To the resulting filtrate was added 20 ml of chloroform, and the product and the starting materials were extracted. The organic layer was washed with

saturated brine, dried over anhydrous magnesium sulfate, and after filtration, the organic layer was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica gel column chromatography (~~Wakogel~~ WAKOGEL C-200 (trade name), chloroform/methanol=98/2 to 80/20 (volume ratio)) to obtain 40.2 mg (Isolated yield based on methyl (±)-3-benzylamino-3-(4-fluorophenyl)propionate=40.2%) of methyl (R)-3-benzylamino-3-(4-fluorophenyl)propionate and 39.9 mg (Isolated yield based on methyl (±)-3-benzylamino-3-(4-fluorophenyl)propionate=42.0%) of (S)-3-benzylamino-3-(4-fluorophenyl)propionic acid.

Amend the paragraph beginning at line 33 at page 72 and ending at line 12 at page 73 as follows:

Analytical conditions of high performance liquid chromatography;

Methyl 3-benzylamino-3-(4-fluorophenyl)propionate

Column: ~~chiral-pack~~ CHIRAL PACK AS (0.46 cmΦ x 25 cm, available from DAICEL CHEMICAL INDUSTRIES, LTD.)

Solvent: hexane/isopropyl alcohol (=9/1 (volume ratio))

Flow rate: 0.5 ml/min

Temperature: 30°C

3-Benzylamino-3-(4-fluorophenyl)propionic acid

Column: ~~chiral~~ CHIRAL CD-Ph (0.46 cmΦ x 25 cm, available from SHISEIDO CO., LTD.)

Solvent: acetonitrile/water (=1/9 (volume ratio))

Potassium dihydrogen phosphate 40 mM

pH 3.5

Flow rate: 0.5 ml/min

Temperature: 25°C

Amend the paragraph beginning at line 4 and ending at line 29 at page 74 as follows:

To a mixed solvent of 1 mL of cyclohexane and 1 mL of water was added 100 mg of methyl (±)-3-benzylamino-3-(4-fluorophenyl)propionate, and the mixture was maintained at 30°C. To the resulting mixture was added 5 mg of lipase (CAL; available from Roche, ~~Chirazyme~~ CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 58 hours, at the time when the conversion rate of the starting materials reached 48.0%, 2 mol/L of hydrochloric acid was added to the reaction mixture to adjust a pH to 1, filtered through Celite (No. 545), and washed with 5 ml of chloroform. To the resulting filtrate was added 20 mol of chloroform, and the product and the starting materials were extracted. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and after filtration, the organic layer was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica gel column chromatography (~~Wakogel~~ WAKOGEL C-200 (trade name), chloroform/ methanol=98/2 to 80/20 (volume ratio)) to obtain 41.0 mg (Isolated yield based on methyl (±)-3-benzylamino-3-(4-fluorophenyl)propionate=41.0%) of methyl (R)-3-benzylamino-3-(4-fluorophenyl)propionate and 36.6 mg (Isolated yield based on methyl (±)-3-

benzylamino-3-(4-fluorophenyl)propionate=38.5%) of (S)-3-benzylamino-3-(4-fluorophenyl)-propionic acid.

Amend the paragraph beginning at line 2 and ending at line 17 at page 75 as follows:

Analytical conditions of high performance liquid chromatography;

Methyl 3-benzylamino-3-(4-fluorophenyl)propionate

Column: ~~chiral pack~~ CHIRAL PACK AS (0.46 cm Φ x 25 cm, available from DAICEL
CHEMICAL INDUSTRIES, LTD.)

Solvent: hexane/isopropyl alcohol (=9/1 (volume ratio))

Flow rate: 0.5 ml/min

Temperature: 30°C

3-Benzylamino-3-(4-fluorophenyl)propionic acid

Column: ~~chiral~~ CHIRAL CD-Ph (0.46 cm Φ x 25 cm, available from SHISEIDO CO., LTD.)

Solvent: acetonitrile/water (=1/9 (volume ratio))

Potassium dihydrogen phosphate 40 mM

pH 3.5

Flow rate: 0.5 ml/min

Temperature: 25°C

Amend the paragraph beginning at line 22 at page 75 and ending at line 6 at page 76 as follows:

To 4 mL of water were added 400 mg (1.28 mmol) of methyl (\pm)-3-benzylamino-3-(3,4-methylenedioxyphenyl)propionate and 107 mg (1.28 mmol) of sodium hydrogen carbonate, and the mixture was maintained to 30°C. To the resulting mixture was added 2 mg of lipase (CAL; available from Roche, Chirazyme CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 20 hours, at the time when the conversion rate of the starting materials reached 46.2%, 8 ml of ethyl acetate and 112 mg of sodium hydrogen carbonate were added to the reaction mixture and the aqueous layer was extracted. The resulting aqueous layer was adjusted to an inner pH of 2.0 with 2 mol/L of hydrochloric acid aqueous solution, and 8 ml of ethyl acetate and 500 mg of sodium chloride were added to the mixture to extract the organic layer. The resulting organic layer was dried over magnesium sulfate, filtered and concentrated to obtain 135 mg (Isolated yield based on methyl (\pm)-3-benzylamino-3-(4-fluorophenyl)propionate= 35.3%) of (R) or (S)-3-benzylamino-3-(3,4-methylenedioxyphenyl)propionic acid as white crystal.

Amend the paragraph beginning at line 11 and ending at line 21 at page 76 as follows:

Analytical conditions of high performance liquid chromatography;
3-(R) or (S)-benzylamino-3-(3,4-methylenedioxyphenyl)propionic acid
Column: ~~chiral~~ CHIRAL CD-Ph (0.46 cm Φ x 25 cm, available from SHISEIDO CO., LTD.)

Solvent: acetonitrile/water (=1/9 (volume ratio))

Potassium dihydrogen phosphate 40 mM

pH 3.5

Flow rate: 0.5 ml/min

Temperature: 25°C

Amend the paragraph beginning at line 34 at page 76 and ending at line 13 at page 77 as follows:

To 37 mL of water were added 7.49 g (23.9 mmol) of methyl (\pm)-3-benzylamino-3-(3,4-methylenedioxyphenyl)propionate and 1.00 g (12.0 mmol) of sodium hydrogen carbonate, and the mixture was maintained at 30°C. To the resulting mixture was added 37.5 mg of lipase (CAL; available from Roche, ~~Chirazyme~~ CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 24 hours, at the time when the conversion rate of the starting materials reached 29.1%, 40 ml of toluene was added to the reaction mixture. After the resulting mixture was stirred for 15 minutes at room temperature, the mixture was filtered and dried to obtain 1.52 g (Isolated yield based on methyl (\pm)-3-benzylamino-3-(4-fluorophenyl)propionate= 21.2%) of 3-(R) or (S)-benzylamino-3-(3,4-methylenedioxyphenyl)propionic acid as white crystal.

Amend the paragraph beginning at line 22 at page 77 and ending at line 1 at page 78 as follows:

To 372 mL of water were added 37.20 g (0.13 mol) of methyl (\pm)-3-benzylamino-3-(p-tolyl)propionate and 11.03 g (0.13 mol) of sodium hydrogen carbonate, and the mixture was maintained at 30°C. To the resulting mixture was added 186 mg of lipase (CAL; available from Roche, Chirazyme CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 8.5 hours, at the time when the conversion rate of the starting materials reached 39.4%, the reaction mixture was filtered to obtain a solid state product. To the resulting product was added 200 ml of toluene and the mixture was stirred at room temperature for 2 hours, then, filtered and dried to obtain 11.11 g (Isolated yield based on methyl (\pm)-3-benzylamino-3-(4-fluorophenyl)propionate= 31.4%) of 3-(R) or (S)-benzylamino-3-(p-tolyl)propionic acid as white crystal.

Amend the paragraph beginning at line 6 and ending at line 15 at page 78 as follows:

Analytical conditions of high performance liquid chromatography;
3-(R) or (S)-benzylamino-3-(p-tolyl)propionic acid
Column: ~~chiral~~ CHIRAL CD-Ph (0.46 cm Φ x 25 cm, available from SHISEIDO CO., LTD.)
Solvent: acetonitrile/water (=1/9 (volume ratio))
Potassium dihydrogen phosphate 40 mM
pH 3.5

Flow rate: 0.5 ml/min

Temperature: 25°C

Amend the paragraph beginning at line 29 at page 78 and ending at line 16 of page 79 as follows:

To 1 mL of 0.1 mol/L aqueous sodium phosphate solution with a pH of 8.0 was added 50.0 mg of methyl (±)-N-benzylhomopipicolate, and the mixture was maintained at 30°C. To the resulting mixture was added 2 mg of lipase (CAL; available from Roche, Chirazyme CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 110 minutes, at the time when the conversion rate of the starting materials reached 41.6%, 2 mol/L of hydrochloric acid was added to the reaction mixture to adjust a pH to 1, filtered through Celite (No. 545), and washed with 5 ml of methanol. To the resulting filtrate was added 20 ml of chloroform, and the product and the starting materials were extracted. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and after filtration, the organic layer was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica gel column chromatography (Wakogel WAKOGEL C-200 (trade name), chloroform/methanol=98/2 to 80/20 (volume ratio)) to obtain 18.6 mg (Isolated yield based on methyl (±)-N-benzylhomopipicolate=37.2%) of methyl (S)-N-benzylhomopipicolate and 21.7 mg (Isolated yield based on methyl (±)-N-benzylhomopipicolate=45.2%) of (R)-N-benzylhomopipicolic acid.

Amend the paragraph beginning at line 25 at page 79 and ending at line 4 at page 80 as follows:

Analytical conditions of high performance liquid chromatography;

Methyl N-benzylhomopiecolate

Column: ~~chiral pack~~ CHIRAL PACK AS (0.46 cm Φ x 25 cm, available from DAICEL
CHEMICAL INDUSTRIES, LTD.)

Solvent: hexane/isopropyl alcohol (=9/1 (volume ratio))

Flow rate: 0.5 ml/min

Temperature: 30°C

N-benzylhomopiecolic acid

Column: ~~chiral~~ CHIRAL CD-Ph (0.46 cm Φ x 25 cm, available from SHISEIDO CO., LTD.)

Solvent: acetonitrile/water (=1/9 (volume ratio))

Potassium dihydrogen phosphate 40 mM

pH 3.5

Flow rate: 0.5 ml/min

Temperature: 25°C

Amend the paragraph beginning at line 25 at page 80 and ending at line 12 at page 81 as follows:

Incidentally, absolute configuration of the optically active N-benzylhomopipicolinic acid was determined as follows. That is, 100 mg of the optically active N-benzylhomopipicolinic acid having an optical purity of 96.7%*ee* obtained by the operation of Example 1 was dissolved in 2 mL of methanol, 23.2 mg of 20% palladium/carbon powder was added to the solution, and the mixture was reacted at room temperature while stirring. After 1 hour, the reaction mixture was filtered through Celite (No. 545), and washed with 5 ml of methanol. The resulting filtrate was concentrated under reduced pressure to obtain an oily substance. This oily substance was purified by silica gel column chromatography (~~Wakogel~~ WAKOGEL C-200 (trade name), chloroform/ methanol=98/2 to 0/100 (volume ratio)) to obtain 51.3 mg (Isolated yield based on optically active N-benzylhomopipicolinic acid=85.0%) of optically active homopipicolinic acid. Absolute configuration was determined by comparing the specific rotatory power ($[\alpha]_D^{23}$ -54.8° (C 1.30, H₂O)) of the resulting optically active homopipicolinic acid and a sign (literal value $[\alpha]_D^{25}$ +22.1° (C 0.6, H₂O)) of the specific rotatory power of (R)-homopipicolinic acid described in *Synth. Comm.*, 7(4), 239 (1977). Example 15 (Syntheses of methyl (S)-N-benzylhomopipicolate and (R)-N-benzylhomopipicolinic acid)

Amend the paragraph beginning at line 13 and ending at line 36 at page 81 as follows:

To a mixed solvent of 1 mL of cyclohexane and 1 mL of water was added 100 mg of methyl (\pm)-N-benzylhomopiecolate, and the mixture was maintained at 30°C. To the resulting mixture was added 10 mg of lipase (CAL; available from Roche, ~~Chirazyme~~ CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 7 hours, at the time when the conversion rate of the starting materials reached 50.1%, 2 mol/L of hydrochloric acid was added to the reaction mixture to adjust a pH to 1, filtered through Celite (No. 545), and washed with 5 ml of methanol. To the resulting filtrate was added 20 ml of chloroform, and the product and the starting materials were extracted. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and after filtration, the organic layer was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica gel column chromatography (~~Wakogel~~ WAKOGEL C-200 (trade name), chloroform/methanol=98/2 to 80/20 (volume ratio)) to obtain 42.2 mg (Isolated yield based on methyl (\pm)-N-benzylhomopiecolate=42.2%) of methyl (S)-N-benzylhomopiecolate and 39.7 mg (Isolated yield based on methyl (\pm)-N-benzylhomopiecolate=41.3%) of (R)-N-benzylhomopiecolic acid.

Amend the paragraph beginning at line 9 and ending at line 24 at page 82 as follows:

Analytical conditions of high performance liquid chromatography;

Methyl N-benzylhomopiecolate

Column: ~~chiral-pack~~ CHIRAL PACK AS (0.46 cm Φ x 25 cm, available from DAICEL
CHEMICAL INDUSTRIES, LTD.)

Solvent: hexane/isopropyl alcohol (=9/1 (volume ratio))

Flow rate: 0.5 ml/min

Temperature: 30°C

N-benzylhomopiecolic acid

Column: ~~chiral~~ CHIRAL CD-Ph (0.46 cm Φ x 25 cm, available from SHISEIDO CO., LTD.)

Solvent: acetonitrile/water (=1/9 (volume ratio))

Potassium dihydrogen phosphate 40 mM

pH 3.5

Flow rate: 0.5 ml/min

Temperature: 25°C

Amend the paragraph beginning at line 29 at page 82 and ending at line 16 at page 83 as follows:

To a mixed solvent of 4 mL of cyclohexane and 4 mL of water was added 800 mg of methyl (\pm)-N-benzylhomopiecolate, and the mixture was maintained at 30°C. To the resulting

mixture was added 40 mg of lipase (CAL; available from Roche, ~~Chirazyme~~ CHIRAZYME L-2 (trade name)) originated from *Candida antarctica* at the same temperature, and the mixture was reacted at 30°C while stirring. After 5 hours, at the time when the conversion rate of the starting materials reached 49.7%, 2 mol/L of hydrochloric acid was added to the reaction mixture to adjust a pH to 1, filtered through Celite (No. 545), and washed with 5 ml of methanol. To the resulting filtrate was added 30 ml of chloroform, and the product and the starting materials were extracted. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and after filtration, the organic layer was concentrated under reduced pressure to obtain an oily substance. The resulting oily substance was purified by silica gel column chromatography (Wakogel WAKOGEL C-200 (trade name), chloroform/methanol=98/2 to 80/20 (volume ratio)) to obtain 359 mg (Isolated yield based on methyl (±)-N-benzylhomopiecolate=43.1%) of methyl (S)-N-benzylhomopiecolate and 314 mg (Isolated yield based on methyl (±)-N-benzylhomopiecolate=40.8%) of (R)-N-benzylhomopiecolic acid.

Amend the paragraph beginning at line 25 of page 83 and ending at line 4 at page 84 as follows:

Analytical conditions of high performance liquid chromatography;
methyl N-benzylhomopiecolate
Column: ~~chiral pack~~ CHIRAL PACK AS (0.46 cmΦ x 25 cm, available from DAICEL
CHEMICAL INDUSTRIES, LTD.)
Solvent: hexane/isopropyl alcohol (=9/1 (volume ratio))

Flow rate: 0.5 ml/min

Temperature: 30°C

N-benzylhomopiperic acid

Column: ~~ehiral~~ CHIRAL CD-Ph (0.46 cm Φ x 25 cm, available from SHISEIDO CO., LTD.)

Solvent: acetonitrile/water (=1/9 (volume ratio))

Potassium dihydrogen phosphate 40 mM

pH 3.5

Flow rate: 0.5 ml/min

Temperature: 25°C

Amend the paragraph beginning at line 2 and ending at line 23 at page 86 as follows:

In 13 ml of acetonitrile was dissolved 1.0 g (5.16 mmol) of 2-carbomethoxymethylpiperidine hydrochloride, and 1.77 ml (12.72 mmol) of triethylamine and 0.76 ml (6.36 mmol) of benzyl bromide were added to the solution at room temperature, and the resulting mixture was reacted at the same temperature under stirring for 5 hours. After completion of the reaction, the obtained reaction mixture was filtered and then concentrated under reduced pressure, then, 25 ml of ethyl acetate and 15 ml of a saturated aqueous sodium hydrogen carbonate solution were added to the residue and the organic layer was extracted. The obtained organic layer was washed with 15 ml of a saturated aqueous sodium hydrogen carbonate solution, and saturated saline solution, dried over anhydrous magnesium sulfate, then, filtered and the filtrate was concentrated under reduced pressure to obtain 0.97 g of an oily

substance. The resulting oily substance was purified by silica gel column chromatography (~~Wakogel~~ WAKOGEL C-200 (trade name), n-hexane/ethyl acetate =4/1(volume ratio)) to obtain 0.75 g (Isolated yield based on 2-carbomethoxymethylpiperidine hydrochloride=59%) of N-benzyl-2-carbomethoxymethylpiperidine.